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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/002,413	01/02/1998	RICHARD C. ALLEN	311772000500	7792

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/002,413	ALLEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,57,62,63 and 70-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,57,62,63 and 70-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-28-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10-28-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-55, 58-61, 64-69 have been canceled. Claims 56, 57, 62, 63 and 70-73 remain pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Rejections - 35 USC 112

Enablement

Claims 56, 57, 62, 63 and 70-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal, does not reasonably provide enablement for administering RPE and non-RPE as claimed to increase survival of the non-RPE in the mammal as broadly claimed or to use RPE and non-RPE, specifically RPE and insulin producing β-cells as claimed, to treat a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 56, 57, 70 and 71 are directed toward a pharmaceutical composition comprising RPE and insulin-producing β cells. Claims 62 and 63 are directed toward a kit comprising RPE and insulin-producing β cells.

The enablement rejection regarding claims 56, 57, 62, 63, 70 and 71 has been withdrawn because the phrases "pharmaceutical composition" and "kit" are not limited to compositions comprising RPE and β cells capable of treating disease. Pancreatic Islet of Langerhans β cells can be co-cultured with other cells in vitro as shown by Selawry (col. 21, lines 1-5). The effect of insulin secretagogues was tested on islets cultured with and without Sertoli cells. The cells in media meet the limitation of a "pharmaceutical composition" as claimed because they have a physiological pH and are physiologically acceptable.

Claims 72 and 73 remain rejected under enablement. The claims are directed toward an article of manufacture comprising RPE and insulin-producing β cells and packaging material that contains a label indicating that said RPE cells can be used for facilitating survival of an allogeneic graft of the non-RPE cell population in a mammal.

RPE and pancreatic β cells can be used to treat diabetes by obtaining therapeutic levels of insulin secreted by the β cells (pg 4, line 20; claims 56, 57, 62, 63 and 70-73).

Cherksey of record (US Patent 5,618,531) taught that symptoms of Parkinson's disease were treated using RPE cells supported by a matrix transplanted into the brain of rats (see the claims, especially claim 13, see also col. 17, line 27., col. 18, lines 25-

44 and col. 19, line 24). Cherksey did not teach co-administering RPE and non-RPE cells; however, Cherksey suggests transplanting a matrix having both RPE and non-RPE cells, such as glial cells (col. 9, line 2, col. 11, line 37).

Selawry (1993, Cell Trans., Vol. 2, pg 123) and Selawry (US Patent 5,725,854) taught administering Sertoli cells and pancreatic islet β-cells such that the Sertoli cells create an immune-privileged site and the islet cells produce therapeutic levels of a biological molecule.

Fraser of record (1995, Cell Transplantation, Vol. 4, pg 529-534) taught Islet of Langerhans β-cells encapsulated in a biocompatible membrane maintained in vitro. Fraser stated the potential of membrane encapsulated pancreatic islets for transplantation was well-described.

In addition, the art at the time of filing taught administering pancreatic islet β-cells into mammals to produce insulin (Sigalla of record, Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634; pg 1626, col. 2, 2nd and 3rd ¶; pg 1628, col. 1, 4th ¶ and col. 2, 4th and 5th full ¶; Weber of record, 1997, J. Surg. Res., Vol. 69, pg 23-32; pg 25, col. 1, "Islet transplantation"; pg 27, ¶ bridging col. 1-2).

While RPE were known to provide "immune privilege" in the eye (Ye of record, 1993, Current Eye research, Vol. 12, pg 629-639; pg 629, col. 1, line 1; pg 630, col. 2, line 24; last line of abstract and pg 631, col. 2, line 20), the art at the time of filing did not teach RPE could provide "immune privilege" when transplanted. Nor did the art teach the structure of a site resulting from administering RPE to a mammal. The art did not define the immune response to such a site or teach how to increase survival of non-

RPE in a mammal using RPE. Therefore, it was unpredictable at the time of filing how to increase survival of pancreatic β-cells in a mammal using RPE as claimed. Nor did the art at the time of filing teach therapeutic levels of insulin could be secreted by pancreatic β-cells from within an immune privileged site created by RPE. Therefore, it was also unpredictable at the time of filing how to a therapeutic effect from insulin secreted from pancreatic β-cells within an immune privileged site made by RPE cells.

The specification demonstrates isolating and culturing fetal RPE *in vitro* (pg 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pg 21-27). The specification suggests treating a number of diseases (pg 1, line 23; pg 3, line 26; pg 5, line 31), delivering RPE to any of a number of tissues (pg 15, line 7), administering RPE and non-RPE as a single composition or as separate compositions (pg 4, line 23) and using non-RPE such as endocrine cells that produce a functionally active therapeutic molecule (sentence bridging pg 6-7). The specification does not teach administering RPE cells with non-RPE cells to a mammal, obtaining a therapeutic effect by administering RPE and non-RPE cells or increasing the survival time of non-RPE using RPE.

The specification does not enable administering RPE and non-RPE to a mammal such that survival of the graft is facilitated or such that a therapeutic effect is obtained as claimed. A mere suggestion to increase the survival of allogeneic cells or to treat disease in a mammal by administering the allogeneic cells in combination with RPE is inadequate to overcome the unpredictability in the art to use the claimed invention to increase the survival of the non-RPE or to treat disease. The specification does not

teach the structure obtained upon administering RPE and non-RPE, the immune response to such a site, the level of secretion of molecules produced by the non-RPE, or treating disease using such a method. The specification does not teach the immune response to such a site or rate of survival of the allogeneic non-RPE cells. The specification does not teach administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal. Therefore, the specification does not overcome the unpredictability in the art by teaching how to use RPE and allogeneic non-RPE to increase survival of the non-RPE or to secrete therapeutically effective amounts of a biologically active molecule from non-RPE in such a site.

Specifically, the specification does not provide any guidance on how to use allogeneic pancreatic islet of Langerhans cells (claims 57, 63, 73) or insulin-producing cells (claim 56, 62, 72) in combination with RPE to treat disease. While Selawry taught using Sertoli cells to deliver β-cells secreting insulin, the specification does not provide adequate correlation between Sertoli cells and RPE such that similar results could be obtained. Pg 3, line 23, states Sertoli cells secrete FasL. But the specification does not teach RPE secrete the same amount of FasL, that the structure of the site created by Sertoli cells and RPE is the same, that biological molecules secrete through a structure created by RPE or that the amount of secretion of a therapeutic protein obtained using RPE cells would be equivalent to that observed using Sertoli cells.

Applicants argue the specification teaches RPE cells secrete substantial amounts of biologically active FasL on pg 16, lines 18-25, and pg 24-28. Applicants argue the specification teaches RPE conditioned medium induced apoptosis in

thymocytes on pg 27, lines 15-37. Therefore, applicants conclude the number of RPE cells needed to provide an immune privileged site and increase survival time of the non-RPE cells can be determined. Applicants argue the specification demonstrates that RPE cells secrete substantial amounts of biologically active FasL sufficient to induce apoptosis in fetal thymocytes, pre-T cells which exist in a high activation state. Given the teaching that RPE cells secrete biologically active F%L in easily measurable amounts, Applicants submit that the number of RPE cells needed to prolong survival time of insulin-producing β cells can be determined by the skilled artisan without undue experimentation. Applicants' argument is not persuasive.

One of skill would not conclude that RPE cells would create an immune privileged site simply because FasL was produced by RPE cells *in vitro*; at least a showing that the amount of FasL produced in RPE and Sertoli cells was the same *in vitro* would be required (Sertoli cells being known to create an immune privileged site). One of skill would not conclude that RPE cells created an immune privileged site because RPE conditioned medium induced apoptosis in thymocytes; other components of the immune system would have to be considered. For example, antibodies may not be affected by FasL and would not be subject to apoptosis because they are not cells. Applicants have not shown that any reasonable number of RPE cells would secrete amounts of FasL similar to those of Sertoli cells known to provide immune privileged sites for insulin secreting β cells or that insulin could be secreted through the immune privileged site made with RPE cells. The description of the amounts of RPE to use on pg 15, lines 18-30, are generic and do not provide any guarantee that the amounts of

RPE capable of "achieving the purposes of the present invention" exist. Without such guidance, it would require one of skill undue experimentation to determine how to use the RPE cells to facilitate survival of an allogeneic graft of insulin producing β-cells in a mammal.

Indefiniteness

The rejection of claims 41, 42, 44-46, 48-50, 65, 66, 68 and 69 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record has been withdrawn because the claims have been canceled.

Claim Rejections - 35 USC 103

The rejection of claims 41, 42, 44-46, 48, 49, 65, 68 and 69 under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record as supported by Jorgensen (1997, Invest. Ophthalmology and Visual Sci., Vol. 38, No. 4, part 1-2, pg 2186, Abstract 924) has been withdrawn because the claims have been canceled. The rejection of claims 70 and 71 has been withdrawn. It is readily apparent that claims 70 and 71 were included in the rejection by mistake because they were dependent upon claim 56, which was not included in the rejection.

Claims 56, 57, 62, 63 and 70-73 are free of the prior art because the prior art did not teach or suggest a composition comprising RPE cells and pancreatic β cells as claimed.

Selawry (1993, Cell Trans., Vol. 2, pg 123) and Selawry (US Patent 5,725,854), both of record, described combining Sertoli cells and pancreatic islet β-cells such that the Sertoli cells create an immune-privileged site upon being administered to a subject. Cherksey of record (US Patent 5,618,531) taught that symptoms of Parkinson's disease were treated using RPE cells alone (see the claims, especially claim 13, see also col. 17, line 27., col. 18, lines 25-44 and col. 19, line 24). Cherksey suggested transplanting both RPE and non-RPE cells, such as glial cells (col. 9, line 2, col. 11, line 37). However, Cherksey did not teach RPE could create an immune privileged site for delivery of non-RPE cells like the Sertoli cells described by Selawry. It would have required hindsight reasoning to replace Sertoli cells capable of creating an immune privileged site with RPE cells to make an obviousness rejection based on Selawry.

Cherksey of record (US Patent 5,618,531) taught that symptoms of Parkinson's disease were treated using RPE cells alone (see the claims, especially claim 13, see also col. 17, line 27, col. 18, lines 25-44 and col. 19, line 24) and suggested transplanting both RPE and non-RPE cells, such as glial cells (col. 9, line 2, col. 11, line 37). One of ordinary skill in the art at the time of filing would have recognized the desire to administer pancreatic β cells with other cells or a membrane that provides immune privilege. However, Cherksey did not teach RPE could create an immune privileged site for non-RPE cells. Therefore, those of ordinary skill in the art at the time the invention

was made would not have recognized that RPE could be used to administer a pancreatic β cell to a subject so that the cell was protected from the immune system of the subject. Nor would those of skill have recognized that the glial cell suggested by Cherksey could be replaced with a pancreatic β cell because the teachings of Cherksey were limited to neural cells and neurological disorders. It would have required hindsight reasoning to replace the glial cells suggested by Cherksey with pancreatic β cells as claimed to make an obviousness rejection based on Cherksey. See response filed 9-13-1999 on pg 10 where it addresses the 103 rejection of claim 22.

Lau (Science, 1996, Vol. 273, pg 109-112), provided in the IDS filed 10-28-04, has been considered. Lau taught transplanting islet of Langerhans cells with myoblasts transfected with a vector expressing FasL. It would have required hindsight reasoning to replace the myoblasts transfected with a vector encoding FasL with RPE.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

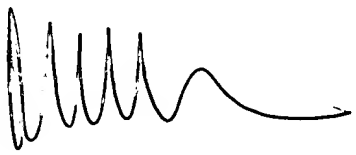
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER